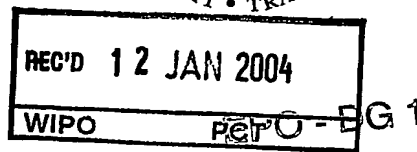




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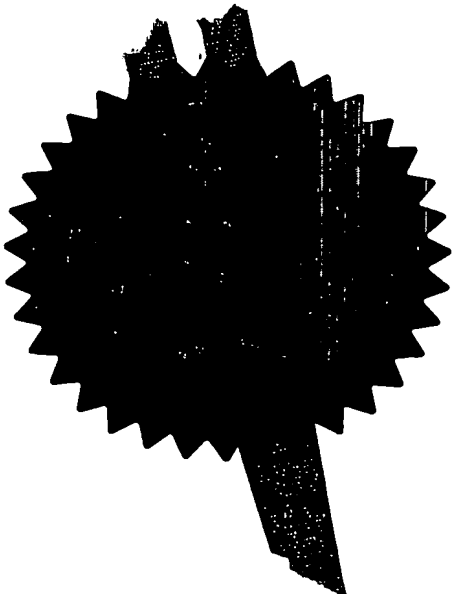
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1. Your Reference

CGP/PG4977 NEWPORT

2. Patent application number

(The Patent office will fill in this part)

0225621.2

02 NOV 2002

3. Full name, address and postcode of the or of each applicant (underline all surnames)

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04NOV02 E760709-1 D10009
P01/7700 0-00-0225621.2

Patents ADP number (if you know it)

473587003

If the applicant is a corporate body, give the country/state of its corporation

4 Title of the invention

MEDICAMENT CARRIER

5 Name of your agent (if you have one)

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Patents ADP number (if you know it)

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Country

Priority application number
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Date of Filing
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Number of earlier application

Date of filing
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8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if:

YES

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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Description 18

Claim(s) 1

Abstract 0

Drawing(s) 2

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Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patent Form 9/77*)

Request for substantive examination (*Patent Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application

Signature Christopher Gerard Pike
AGENT FOR THE APPLICANTS

01 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom
Dr. Christopher G. Pike
01628 471869

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Notes

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Medicament carrier

Technical field

5

The present invention relates to a medicament carrier in blister pack form suitable for carrying dry powder form medicament.

Background to the invention

10

The use of medicament dispensers in the administration of medicaments, for example in bronchodilation therapy is well known. Such devices generally comprise a body or housing within which a medicament carrier is located. Known inhalation devices include those in which the medicament carrier is in blister pack form (e.g. an elongate blister strip) containing a number of discrete doses of powdered medicament. In use, the blister pack is typically housed within the dispenser in such a way that the blisters may be transported through the dispenser in indexed fashion to enable accessing of the discrete doses of medicament carried thereby. Such devices usually contain a mechanism of individually accessing the doses contained within the blisters. Known access mechanisms typically comprise either blister piercing means or means to peel a lid sheet away from a base sheet of the blister pack. The powdered medicament can then be accessed and inhaled.

It is desirable that elongate blister strip form medicament carriers for containing medicament in dry powder form have suitable moisture transfer properties. Whilst to an extent, the optimal character of such properties is dependent on the nature of the particular medicament formulation to be carried within the blister it is generally beneficial for the material of the strip and of any seals made thereto to either prevent or at least to significantly slow down moisture ingress to the medicament contained within the blister to prevent the moisture-induced degradation or agglomeration thereof. Reducing moisture permeation reduction to the cavity of the blister pack and

thereby enhancing the stability of the medicament contained therein are particular targets of interest. Efforts therefore continue to be expended in the development of improved strip materials, pack forms and sealing methods.

5 Conventional medicament blister packs typically comprise aluminium foil sheets in both the lid sheet and base sheet components thereof. The aluminium sheets are selected to have sufficient thickness to be substantially free of 'pinhole' imperfections thereby making them essentially impermeable to the transfer of moisture. In developments thereof, laminate form sheets are used for either one or both of the lid
10 and base sheets, which laminates typically comprise a layer of aluminium foil and one or more polymeric layers. Such laminates are typically employed when a 'cold form' sealing method is employed to seal the lid sheet to the base sheet. Polyvinyl chloride (PVC) is conventionally used as the material of the polymeric layer.

15 The Applicants have now appreciated that such polymeric layers act as the principal conduit for moisture ingress to the medicament contained within the blisters. The absolute rate of flow of moisture is dependent on various factors including prevailing environmental conditions, the polymer material and properties of the medicament itself (e.g. hygroscopic or desiccant properties).

20 The Applicants have now found that moisture ingress to the interior of the blister may be reduced by the selection of particular, unconventional polymeric materials for use in the laminate sheets of the blister packs. The Applicants have also found that moisture ingress may also be reduced by the use of polymeric layers in the
25 laminates, which have reduced thickness compared to conventional polymeric layers. Enhancements in the storage stability of dry powder form medicament contained within the blister packs may thereby be achieved.

Summary of the invention

According to one aspect of the invention there is provided a medicament carrier comprising

5

(a) a base sheet in which blisters are formed to define pockets therein;

(b) a lid sheet which is sealable to the base sheet except in the region of the blisters,

10 wherein said base sheet and/or said lid sheet have a laminate structure as particularly defined herein.

A lid sheet and base sheet for use in forming the medicament carrier and having the laminate structure as particularly defined herein are also provided herein.

15

The term medicament carrier is used to define any suitable carrier. In a preferred aspect, the carrier has a multi-blister pack form, particularly a blister strip having multiple distinct blister portions provided along its length. The medicament carrier suitably has multiple distinct (i.e. separate) medicament doses carried thereby, and
20 may for example, be in the form of a blister strip, disk (e.g., Rotadisk™) or other suitable pack form.

Suitably, the medicament carrier is in the form of a peelable blister strip, particularly an elongate form peelable blister strip. Suitably, the peelable strip comprises a base
25 sheet in which blisters are formed to define pockets therein and a lid sheet which is hermetically sealed to the base sheet except in the region of the blisters in such a manner that the lid sheet and the base sheet can be peeled apart. The base and lid sheets are typically sealed to one another over their whole width except for the forward end portions where they are typically not sealed to one another at all. Thus,
30 separate base and lid sheet forward end portions are presented at the end of the strip.

The lid sheet and/or base sheet of the medicament carrier herein are suitably in the form of a laminate, which comprises multiple layers of different materials.

Typically, the base sheet and/or lid sheet herein comprises (a) a first layer of metal foil, particularly aluminium foil; and (b) a second layer of polymeric material. Optionally, other layers are also present.

Suitably, the polymeric material is selected from the group consisting of polypropylene (in oriented or cast form); polyethylene (in high or low density form); and polyvinylidene chloride (PVDC).

In one particular aspect, the lid sheet comprises at least the following successive layers: (a) paper; adhesively bonded to (b) polyester; adhesively bonded to (c) aluminium foil; that is coated with a heat seal lacquer for bonding to the base sheet. The thickness of each layer may be selected according to the desired properties but is typically of the order of from 5 to 200 micron, particularly from 10 to 50 micron.

In another particular aspect, the base sheet comprises at least the following successive layers: (a) oriented polyamide (OPA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) a third layer comprising a polymeric material. The polymeric material is selected from the group consisting of polypropylene (in oriented or cast form); polyethylene (in high or low density form); and polyvinylidene chloride (PVDC). The third layer will bond with the lid sheet and is generally treated with a heat seal lacquer.

The thickness of each layer of the base sheet may be selected according to the desired properties but is typically of the order of from 5 to 200 micron, particularly from 10 to 50 micron. Suitably, the thickness of the polymeric layer is minimised to reduce moisture ingress, and particularly is from 20 to 30 micron.

One particular base sheet comprises the following successive layers: (a) oriented polyamide (OPA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) oriented polypropylene. The thickness of the polymeric layer is from 10 to 50 micron, particularly from 20 to 30 micron.

5

Another particular base sheet comprises the following successive layers: (a) oriented polyamide (POA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) cast polypropylene. The thickness of the polymeric layer is from 10 to 50 micron, particularly from 20 to 30 micron.

10

A further particular base sheet comprises the following successive layers: (a) oriented polyamide (POA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) high density polyethylene (HDPE). The thickness of the polymeric layer is from 10 to 50 micron, particularly from 20 to 30 micron.

15

A further particular base sheet comprises the following successive layers: (a) oriented polyamide (POA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) low density polyethylene (LDPE). The thickness of the polymeric layer is from 10 to 50 micron, particularly from 20 to 30 micron.

20

A further particular base sheet comprises the following successive layers: (a) oriented polyamide (POA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) polyvinylidene chloride (PVDC). The thickness of the polymeric layer is from 10 to 50 micron, particularly from 20 to 30 micron.

25

Various known techniques can be employed to join the lid and base sheet and hence to seal the blisters. Such methods include adhesive bonding, hot metal bonding, hot metal welding, radio frequency welding, laser welding, ultrasonic welding and hot bar sealing.

30

5 The lid sheet and base sheet herein are particularly sealable by 'cold form' sealing methods, which are conducted at lower temperatures than conventional heat sealing methods. Such 'cold form' sealing methods are of particular utility where the medicament or medicament formulation for containment within the blister is heat sensitive (e.g. degrades or denatures on heating). Suitable 'cold form' sealing methods are conducted at a temperature in the range of 150-250°C, more preferably, 210-240°C.

10 One method for forming a medicament carrier herein comprises the steps of (a) providing a base sheet having a first mating surface and a lid sheet having a second mating surface, the base sheet including at least one blister having a periphery region, the blister being adapted to receive a medicament composition; (b) filling the blister with the pharmaceutical composition; (c) bonding the base sheet to the lid sheet (e.g. by 'cold form' sealing) to create a primary seal therebetween. The
15 medicament carrier can be of any shape, preferably, substantially elongated or substantially circular.

Suitably, the base sheet includes at least a first bonding material disposed on the first mating surface and the lid sheet includes at least a second bonding material
20 disposed on the second mating surface. In one embodiment, one or both of the first or second bonding materials comprises at least one polymeric material. In an additional embodiment, one or both of the first or second bonding material comprises a heat seal lacquer.

25 A suitable manufacturing system herein comprises (a) a base transporter for transporting a base sheet to a filling station, the base sheet including at least one blister adapted to receive a medicament composition, the base sheet further including a first bonding material; (b) a filling apparatus for filling the blister with the medicament composition; (c) a lid transporter for transporting a lid sheet proximate
30 to the filled base sheet, the lid sheet including a second bonding material; (d) a

bonding mechanism for bonding the first and second bonding materials to create a primary seal therebetween.

Suitably, the medicament carrier additionally comprises a desiccant material which is
5 suitably either impregnated therein, or coated thereto. Suitably, the desiccant is selected from the group consisting of silica gel, zeolite, alumina, bauxite, anhydrous calcium sulphate, activated bentonite clay, water-absorbing clay, molecular sieve and any mixtures thereof.

10 Suitably, the medicament carrier controls the ingress or egress of moisture to the (medicament contained within) the blister cavity thereof such that the ambient moisture content within the blister cavity is essentially constant, such as varying by no more than $\pm 20\%$, preferably by less than $\pm 10\%$. Ambient moisture content may for example be measured by Relative Humidity within the blister cavity. The
15 preferred absolute level of moisture content will vary from medicament to medicament but may be readily determined through laboratory testing.

In use, the medicament carrier is suitably receivable by a medicament dispenser that comprises a housing for receipt of the medicament carrier. In one aspect, the
20 medicament dispenser has unitary form and the housing is integral therewith. In another aspect, the medicament dispenser is configured to receive a refill cassette and the housing forms part of that refill cassette.

Suitably, the interior of the housing is shaped, or alternatively provided with specific
25 guiding features, to guide the medicament carrier appropriately into the housing. In particular, the guiding should ensure that the medicament carrier is suitably located to interact with internal mechanisms (e.g. indexing and opening mechanisms) of the housing.

Suitably, the dispenser has an internal mechanism for dispensing the distinct medicament doses carried by the medicament carrier for administration to the patient (e.g. by inhalation). Suitably, the mechanism comprises,

- 5 a) receiving means for receiving the medicament carrier;
- b) release means for releasing a distinct medicament dose from the medicament carrier on receipt thereof by said receiving means;
- 10 c) an outlet, positioned to be in communication with the medicament dose releasable by said release means;
- d) indexing means for individually indexing the distinct medicament doses of the medicament carrier; and

15

The mechanism comprises receiving means (e.g. a receiving station) for receiving the medicament carrier.

The mechanism further comprises release means for releasing a distinct
20 medicament dose from the medicament carrier on its receipt by the receiving station.

The release means can have any suitable form. Where the elongate carrier is in the form of a blister strip, the release means may for example, be a means to rupture or otherwise access the blister. In a particular preferred aspect, where the blister strip is peelably accessible, the release means comprises means for peeling apart the
25 blister strip.

An outlet is positioned to be in communication with the distinct medicament doses releasable by said release means. The outlet may have any suitable form. In one aspect, it has the form of a mouthpiece and in another, it has the form of a nozzle for
30 insertion into the nasal cavity of a patient.

The outlet is preferably a single outlet, which communicates with the distinct medicament dose releasable by said release means via a common air channelling means (e.g. formed as an air-pipe or common manifold). The patient may therefore breathe in through a single outlet, and that breath be transferred through the common channelling means to the released medicament dose, thereby enabling its inhalation. Baffles or other mechanical aids to break up released medicament powder may be incorporated. Venturi channelling of the air flow is also envisaged in embodiments. Helical form channels are envisaged.

- 10 The mechanism also comprises indexing means for individually indexing the distinct medicament doses of the medicament carrier. Said indexing typically happens in sequential fashion, for example accessing dose portions sequentially arranged along the length of the elongate carrier.
- 15 Optionally, the medicament dispenser also includes counting means for counting each time a distinct medicament dose of the medicament carrier is indexed by said indexing means.

In one aspect, counting means is arranged to count each time a distinct medicament dose of the medicament carrier is indexed by said indexing means. Suitably, the indexing means and counting means engage directly or indirectly (e.g. via a coupling) with each other to enable counting of each indexation.

Suitably, the counting means is provided with (or communicates with) a display for displaying to the patient the number of distinct doses left to be taken or the number of doses taken.

In one preferred aspect, the medicament dispenser takes the form of a dispenser for use with a medicament carrier having multiple distinct pockets for containing medicament doses, wherein said pockets are spaced along the length of and defined between two peelable sheets secured to each other, said dispenser having an

internal mechanism for dispensing the medicament doses contained within said medicament carrier, said mechanism comprising,

a) an opening station for receiving a pocket of the medicament carrier;

5 b) peeling means positioned to engage a base sheet and a lid sheet of a pocket which has been received in said opening station for peeling apart such a base sheet and lid sheet, to open such a pocket, said peeling means including lid driving means for pulling apart a lid sheet and a base sheet of a pocket that has been received at
10 said opening station;

c) an outlet, positioned to be in communication with an opened pocket through which a user can access a medicament dose from such an opened pocket;

15 d) indexing means for individually indexing the distinct pockets of the medicament carrier.

Suitably, the indexing means comprises a rotatable index wheel having recesses therein, said index wheel being engageable with a medicament carrier in use with
20 said medicament dispenser such that said recesses each receive a respective pocket of the base sheet of a blister strip in use with said medicament dispenser.

According to another aspect of the present invention there is provided a medicament dispenser comprising (e.g. loaded with) at least one medicament carrier herein.

25

Brief Description of the Drawings

The invention will now be described with reference to the accompanying drawings in which:

30

Figure 1 shows a perspective view of the form of a medicament carrier of a form suitable for use in accord with the present invention;

Figure 2 shows a top view of the form of a medicament carrier of a form suitable for use in accord with the present invention;

Figure 3 shows a top view of the form of another medicament carrier of a form suitable for use in accord with the present invention; and

Figure 4 shows a cross-sectional side view of the form of a laminate form medicament carrier in accord with the present invention.

Detailed Description of the Drawings

Figure 1 shows a medicament carrier 100 that may be constructed to have a detailed form in accord with the present invention. The medicament carrier comprises a flexible strip 101 defining a plurality of pockets 103, 105, 107 each of which would contain a portion of a dose of medicament which can be inhaled, in the form of powder.

20

The strip comprises a base sheet 109 in which blisters are formed to define the pockets 103, 105, 107 and a lid sheet 111 which is hermetically sealed to the base sheet except in the region of the blisters in such a manner that the lid sheet 111 and the base sheet 109 can be peeled apart. The sheets 109, 111 are sealed to one another over their whole width except for the leading end portions 113, 115 where they are preferably not sealed to one another at all. The lid 111 and base 109 sheets are formed of a laminate and are preferably adhered to one another by heat sealing.

The strip 101 is shown as having elongate pockets 103, 105, and 107 that run transversely with respect to the length of the strip 101. This is convenient in that it

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enables a large number of pockets 103, 105, 107 to be provided in a given strip 101 length. The strip 101 may, for example, be provided with sixty or one hundred pockets but it will be understood that the strip 101 may have any suitable number of pockets.

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Referring now to Fig. 2, there is shown a medicament carrier in the form of a laminate assembly or blister strip 200 viewed from underneath. The blister strip has a substantially elongated shape and includes a plurality of blisters 203, 205, 207 formed in the base 209 thereof adapted to receive a pharmaceutical composition 14, 10 preferably in the form of a dry powder. Each blister 203, 205, 207 has a length l_1 that is preferably from 1.5 to 15.0 mm, more preferably, from 1.5 to 8.0 mm, and in an actual embodiment is equal to 7.5 mm, measured along its longer axis, and a width l_2 that is preferably from 1.5 to 10.0 mm, more preferably, from 1.5 to 8.0 mm, and in an actual embodiment is equal to 4.0 mm, measured along its shorter axis.

15

In the illustrated example of Fig 2, the blister strip 200 has a width of 12.5 mm. The thickness of the base 209 is in the range of 75 to 200 micron. The thickness of the lid is in the range 40 to 100 micron. The combined thickness of the base 209 and lid (not visible) is approximately 115 to 300 micron. The blisters 203, 205, 207 are 20 typically at 7.5 mm spacings along the blister strip 200. Each blister 203, 205, 207 contains an effective dosage of powder, preferably less than 30 mg of powder, more preferably, between 5 – 25 mg of powder, and most preferably, approximately 12.5 mg of powder. Preferably, the powder is an inhalable medicament composition comprising at least one medicament active.

25

Suitable materials are employed to construct the base 209 and lid (not visible). Preferably, the base 209 and lid comprise laminate structures having at least one bonding material on at least one mating surface of either the base 209 or lid. The bonding material(s) preferably comprise at least one polymeric material and a heat 30 seal lacquer (e.g. a vinylic heat seal lacquer).

Referring now to Fig. 4, the lid of the blister pack 400 has a multi-layer structure and comprises the following successive layers: paper 425 adhesively bonded to polyester 427 adhesively bonded to aluminium foil 429 that is coated with a heat seal lacquer 430. The base also has a multi-layer structure and comprises at least the following successive layers: oriented polyamide (OPA) 420 adhesively bonded to aluminium foil 422 adhesively bonded to a third polymer layer 424. The blister pack 400 is filled with medicament 414 in dry powdered form.

It will be appreciated that in variations of the blister pack of Fig. 4 different polymers may be used for the third polymer layer of the base sheet including polypropylene (in oriented or cast form); polyethylene (in high or low density form); and polyvinylidene chloride (PVDC).

In one particular variation, the base sheet of the blister pack of Fig 4 has the following structure: 25 micron layer thickness oriented polyamide (OPA) 420; adhesively bonded to 45 micron thickness aluminium foil 422; adhesively bonded to 30 micron thickness polyvinyl chloride 424.

In another particular variation, the base sheet of the blister pack of Fig 4 has the following structure: 25 micron layer thickness oriented polyamide (OPA) 420; adhesively bonded to 60micron thickness aluminium foil 422; adhesively bonded to 20 micron thickness oriented polypropylene 424.

In another particular variation, the base sheet of the blister pack of Fig 4 has the following structure: 25 micron layer thickness oriented polyamide (OPA) 420; adhesively bonded to 60micron thickness aluminium foil 422; adhesively bonded to 25 micron thickness cast polypropylene 424.

As will be appreciated by one having ordinary skill in the art, various conventional adhesives can be employed to bond the laminate layers within the scope of the

invention. Such adhesives include, but are not limited to, cyanoacrylates, acrylics and polyurethanes.

During a typical blister strip manufacturing process, each blister 412 is filled with a pharmaceutical composition 414 and subsequently heat-sealed at a temperature in the range of 150- 250° C, more preferably, 210° C - 240° C. The sealing temperature and other parameters of the sealing method may be varied including tooling, dwell time, sealing pressure and speed of sealing. The heat-sealing step bonds the mating layers (e.g., PVC 424 and heat seal lacquer 430) of the base and lid to seal each blister 412 and, hence forms a secure container for the pharmaceutical composition 414 contained therein. Ideally, the bonding creates a hermetic seal that is formed. As will be appreciated, hermetically sealing each blister 412 to eliminate the possibility of contamination from the external environment can be an important aspect of the manufacturing process.

Various bonding schemes and patterns have been employed to bond and seal blister strips. Illustrative are the bonding schemes and patterns shown in Figs 2 and 3.

Referring now to Fig. 2, there is shown a bonding scheme that employs substantially uniformly distributed heat across at least one surface of the blister strip 200 to create discrete bond areas of the mating base 209 and lid surfaces. Although various bond patterns can be formed by this bonding scheme (e.g., zig-zag, dot, checkered, etc.), a checkered grid 216 pattern is employed in this example.

As illustrated in Fig. 2, the grid 216 provides a restricted, tortuous path (designated generally by Arrow M) for the ingress of contaminants and/or moisture into the blisters 203, 205, 207. Although generally deemed a cost effective means to substantially reduce or eliminate the ingress of moisture into a laminate assembly, it will be appreciated by those having skill in the art that sealing of a laminate assembly, such as blister strip 200, can be significantly enhanced by providing an additional, substantially continuous "secondary seal" within the edge region(s).

Referring now to Fig. 3, there is shown a further bonding scheme that employs substantially uniformly distributed heat across at least one surface of the blister strip 300 to create discrete bond areas of the mating base 309 and lid surfaces. A knurled form bond pattern 316 is employed in this example. The knurling 316 provides a restricted, tortuous path (designated generally by Arrow M) for the ingress of contaminants and/or moisture into the blisters 303, 305, 307.

The medicament carrier of the invention is suitable for carrying medicament combinations, particularly for the treatment of respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), bronchitis and chest infections.

The term "medicament", as used herein, is meant to mean and include any substance (i.e. compound or composition of matter) which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. The term therefore encompasses substances traditionally regarded as actives, drugs and bioactive agents, as well as biopharmaceuticals

Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (e.g. as the sodium salt), ketotifen or nedocromil (e.g. as the sodium salt); antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatory, e.g., beclomethasone (e.g. as the dipropionate ester), fluticasone (e.g. as the propionate ester), flunisolide, budesonide, rofleponide, mometasone e.g. as the furoate ester), ciclesonide, triamcinolone (e.g. as the acetate) or 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (e.g. as free base or sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), formoterol (e.g. as fumarate), isoprenaline, metaproterenol,

phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone; adenosine 2a agonists, e.g. 2R,3R,4S,5R)-2-[6-Amino-2-(1S-5 hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (e.g. as maleate); α_4 integrin inhibitors e.g. (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidiny]carbonyl}oxy)phenyl]-2-(((2S)-4-methyl-2-{{[2-(2-methylphenoxy) acetyl]amino}pentanoyl}amino] propanoic acid (e.g. as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (e.g. as 10 bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; vaccines, diagnostics, and gene therapies. It will be clear to a person skilled in the art that, where appropriate, the medicaments may 15 be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament.

Preferred components of the combinations comprise medicaments selected from 20 albuterol, salmeterol, fluticasone propionate and beclomethasone dipropionate and salts or solvates thereof, e.g., the sulphate of albuterol and the xinafoate of salmeterol.

Preferred components of combinations of active ingredients contain salbutamol (e.g., 25 as the free base or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) or formoterol (eg as the fumarate salt) in combination with an anti-inflammatory steroid such as a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate) or budesonide. A particularly preferred combination of components comprises fluticasone propionate and salmeterol, or a salt thereof (particularly the 30 xinafoate salt). A further combination of components of particular interest is budesonide and formoterol (e.g. as the fumarate salt).

By the terms "medicament formulation" and "pharmaceutical composition", as used herein, it is meant to mean a combination of at least one medicament and one or more added components or elements, such as an "excipient" or "carrier." As will be appreciated by one having ordinary skill in the art, the terms "excipient" and "carrier" generally refer to substantially inert materials that are nontoxic and do not interact with other components of the composition in a deleterious manner. Examples of normally employed "excipients," include pharmaceutical grades of carbohydrates, including monosaccharides, disaccharides, cyclodextrins and polysaccharides (e.g., dextrose, sucrose, lactose, raffinose, mannitol, sorbitol, inositol, dextrans and maltodextrins); starch; cellulose; salts (e.g., sodium or calcium phosphates, calcium sulfate, magnesium sulfate); citric acid; tartaric acid; glycine; leucine; high molecular weight polyethylene glycols (PEG); pluronics; surfactants; lubricants; stearates and their salts or esters (e.g., magnesium stearate); amino acids; fatty acids; and combinations thereof.

The noted medicaments and excipients may be prepared as composite materials, such as by co-precipitation or by coating, or other method known in the art, or may be prepared from batches of separately prepared individual particles which are subsequently blended together to form particulate mixtures of medicament and excipient particles.

Generally, powdered medicament particles suitable for delivery to the bronchial or alveolar region of the lung have an aerodynamic diameter of less than 10 micrometers, preferably less than 6 micrometers. Other sized particles may be used if delivery to other portions of the respiratory tract is desired, such as the nasal cavity, mouth or throat. The medicament may be delivered as pure drug, but more appropriately, it is preferred that medicaments are delivered together with excipients (carriers) which are suitable for inhalation. Lactose is a preferred excipient.

Particles of the powdered medicament and/or excipient may be produced by conventional techniques, for example by micronisation, milling or sieving. Additionally, medicament and/or excipient powders may be engineered with

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particular densities, size ranges, or characteristics. Particles may comprise active agents, surfactants, wall forming materials, or other components considered desirable by those of ordinary skill.

- 5 The excipient may be included with the medicament via well-known methods, such as by admixing, co-precipitating and the like. Blends of excipients and drugs are typically formulated to allow the precise metering and dispersion of the blend into doses. A standard blend, for example, contains 13000 micrograms lactose mixed with 50 micrograms drug, yielding an excipient to drug ratio of 260:1. Dosage blends
10 with excipient to drug ratios of from 100:1 to 1:1 may be used. At very low ratios of excipient to drug, however, the drug dose reproducibility may become more variable.

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto.

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The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described therein. They may take the form of product, method or use claims and
20 may include, by way of example and without limitation, one or more of the following claims:

Claims

1. A medicament carrier comprising

5 (a) a base sheet in which blisters are formed to define pockets therein;

(b) a lid sheet which is sealable to the base sheet except in the region of the blisters,

wherein said base sheet and/or said lid sheet have a laminate structure comprising

10 (a) a first layer of aluminium foil; and (b) a second layer of polymeric material selected from the group consisting of polypropylene (in oriented or cast form); polyethylene (in high or low density form); and polyvinylidene chloride (PVDC).

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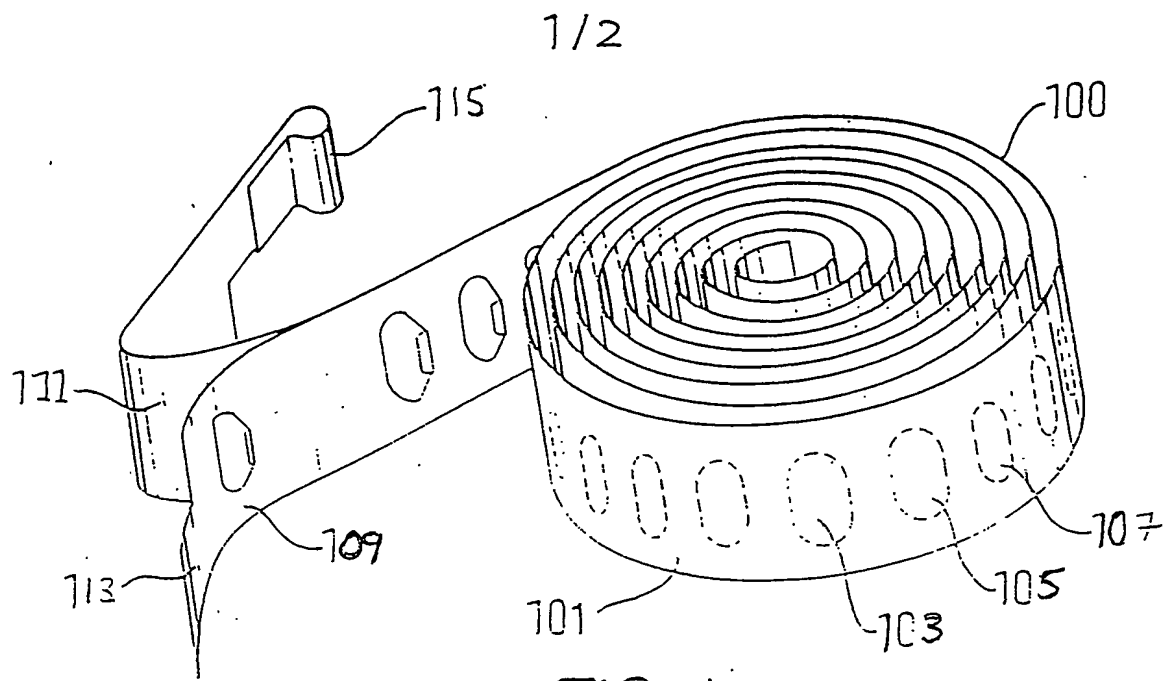


FIG. 1

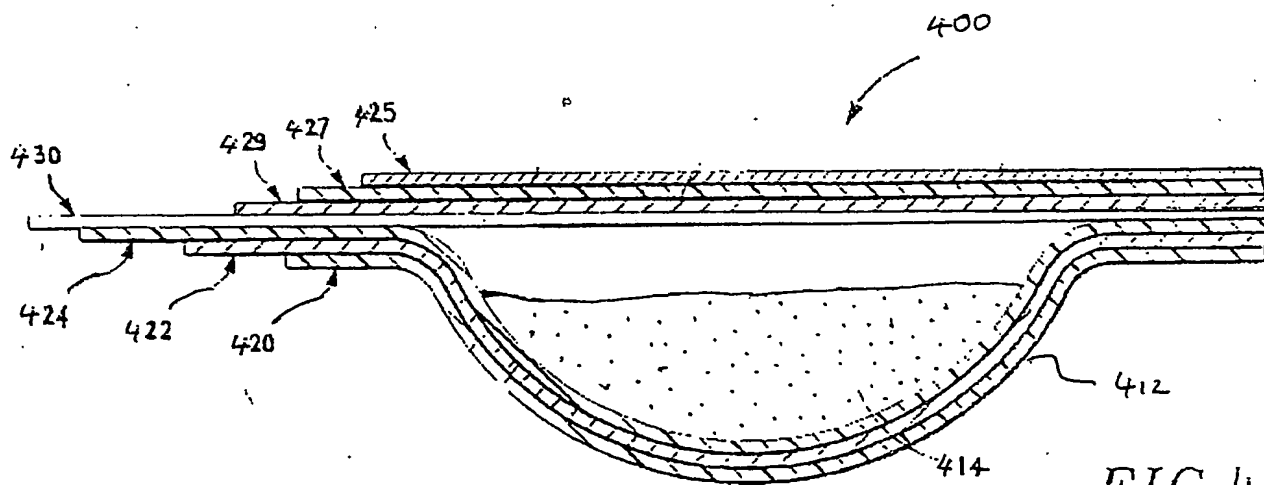


FIG 4

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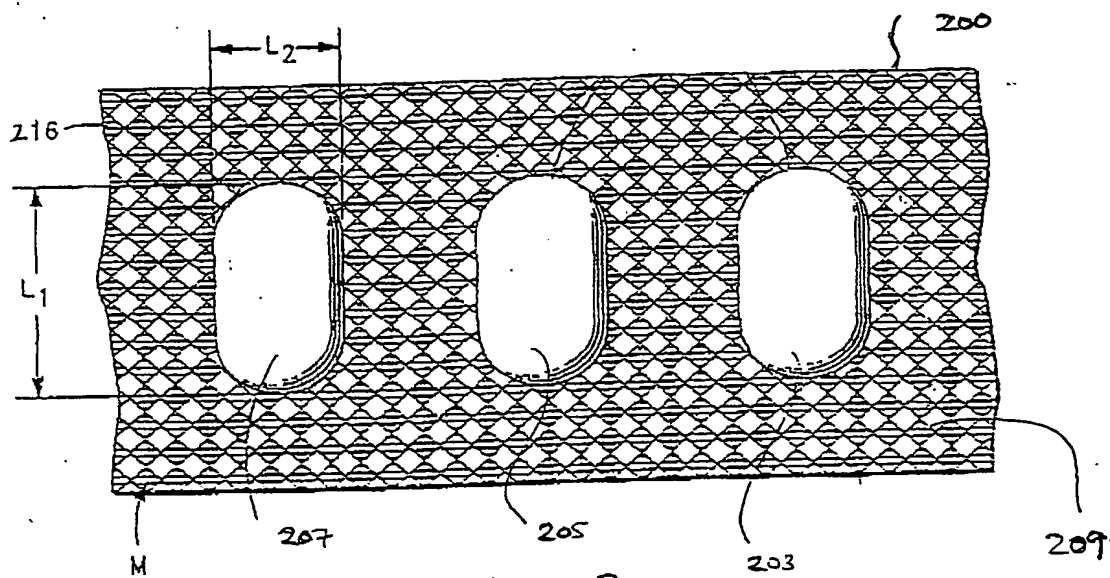


FIG. -2

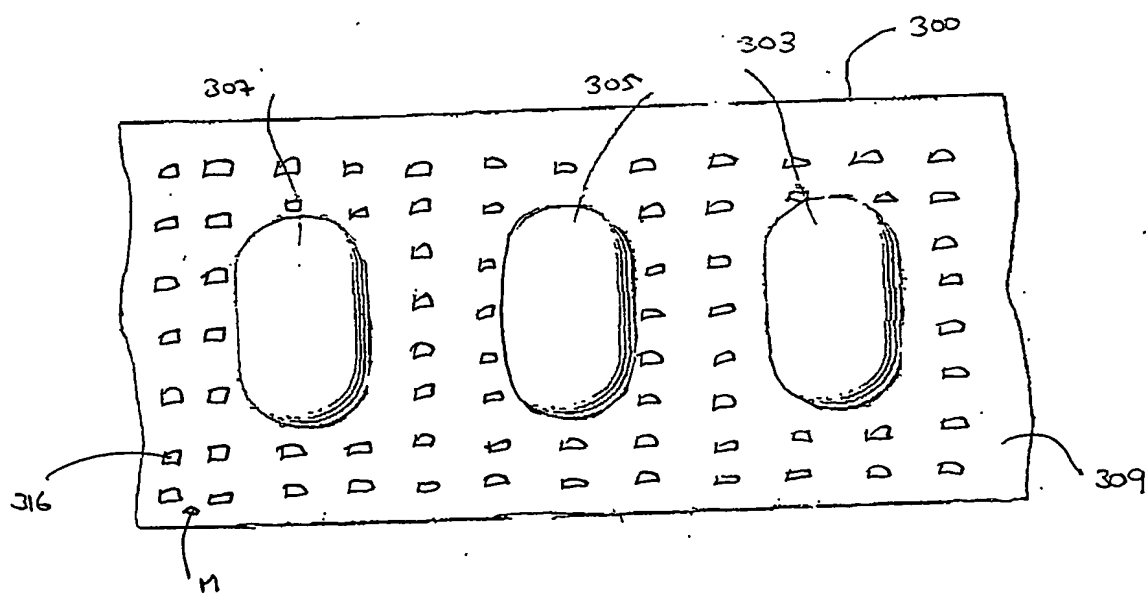


FIG. -3

PCT Application

EP0312159

